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Synaptic Inputs Mediating Bipolar Cell Responses in the Tiger Salamander Retina

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Postsynaptic receptors in bipolar cells were studied by focal application of glutamate and GABA to the outer and inner plexiform layers (OPL and IPL) under visual guidance in living retinal slices of the tiger salamander. Two different types of conductance change could be elicited in bipolar cells by applying glutamate to the OPL. In off-center cells, which had axon telodendria ramifying in the distal 55% of the IPL, glutamate elicited a conductance increase associated with a reversal potential near −5 mV. In on-center cells, which had telodendria stratified in the proximal 45% of the IPL, glutamate caused a conductance decrease associated with a reversal potential near −11 mV. These observations suggest that glutamate gates relatively nonspecific cation channels at synapses between photoreceptors and bipolar cell dendrites. Application of glutamate to the IPL elicited no conductance change in Co^{2+} Ringer's solution, but in normal Ringer's it generated a conductance increase associated with a reversal potential near the chloride equilibrium potential (E_{Cl}). These findings are consistent with the notion that glutamate receptors exist in GABAergic and/or glycinergic amacrine cells, and that glutamate in the IPL depolarizes these cells, causing GABA and/or glycine release and the opening of chloride channels in bipolar cell axon terminals. In Co^{2+} Ringer's, application of GABA at the OPL elicited no conductance changes in bipolar cells, suggesting that GABA receptors do not exist on bipolar cell dendrites. Applied at the IPL, GABA elicited large conductance increases associated with a reversal potential near E_{Cl}. Implications of these results for the functional circuitry of the tiger salamander retina are discussed. Copyright © 1996 Elsevier Science Ltd

Glutamate GABA Hyperpolarizing bipolar cell (HBC) Depolarizing bipolar cell (DBC)
Bipolar cell dendrites Bipolar cell axon terminals

INTRODUCTION

Bipolar cells are central neurons in the vertebrate retina. They relay visual signals from photoreceptors and horizontal cells to amacrine cells and ganglion cells (Dowling, 1987). Bipolar cells are also the first neurons along the visual pathway that exhibit center–surround antagonistic receptive field organization, the basic alphabet for spatial information encoding in the visual system (Kuffler, 1953; Hubel & Wiesel, 1961, 1962; Werblin & Dowling, 1969; Kaneko, 1970). The center inputs to bipolar cells are mediated by photoreceptor synapses made on bipolar cell dendrites. The synapses on on-center bipolar cells (depolarizing bipolar cells, or DBCs) are sign-inverting, whereas those on off-center bipolar cells (hyperpolarizing bipolar cells, or HBCs) are sign-preserving (Wu, 1985; Maple *et al.*, 1994). The surround inputs to bipolar cells are mediated by horizontal cells in the outer retina, and by amacrine cells in the inner retina (Dowling & Werblin, 1969; Dowling, 1987). There are two output synapses made by horizontal cells, one on cone photoreceptors (Baylor *et al.*, 1971; Wu, 1991b), and the other on bipolar cells (Dowling & Werblin, 1969; Lasansky, 1973). Amacrine cells make chemical synapses on bipolar cell axon terminals in the inner plexiform layer (IPL) (Dowling & Werblin, 1969; Wong-Riley, 1974), and the synapses made on HBCs are in sublamina a and those made on DBCs are in sublamina b of the IPL (Famiglietti & Kolb, 1975; Famiglietti *et al.*, 1977). Bipolar cells make output synapses on amacrine cells and ganglion cells, with HBC synapses in sublamina a and DBC synapses in sublamina b (Nelson *et al.*, 1978).

Photoreceptors and bipolar cells use glutamate as their neurotransmitter (Copenhagen & Jahr, 1988; Ehinger *et al.*, 1988; Marc *et al.*, 1990; Tachibana & Okada, 1991; Marc *et al.*, 1995), and subpopulations of horizontal cells and amacrine cells use GABA as their neurotransmitter (Lam & Steinman, 1971; Marc *et al.*, 1978; Wu, 1986). Glutamate receptors in HBCs are primarily the kainate/AMPA type (Slaughter & Miller, 1983a, b; Wu & Yang, 1991), whereas those in DBCs are the L-AP4 type (Slaughter & Miller, 1981; Nawy & Jahr, 1990, 1991; Shiells & Falk, 1990, 1992a, b; Karschin & Wassle, 1990). Glutamate receptors in amacrine cells and ganglion cells have been shown to be the kainate/AMPA and

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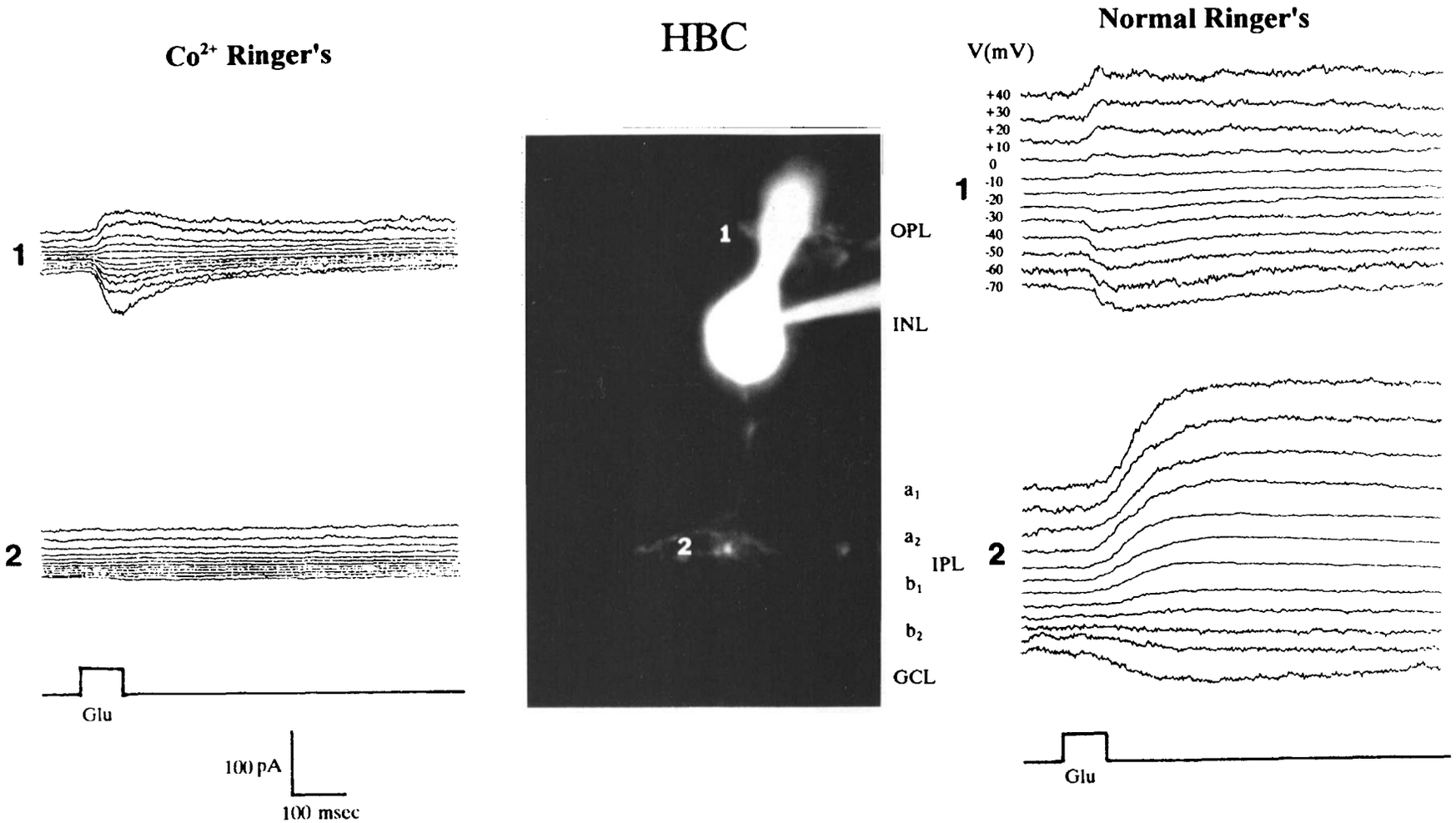

FIGURE 1. Current responses of an off-center bipolar cell (HBC) to focal application of 100 μM glutamate at the OPL (location 1, near the dendrites) and IPL (location 2, near the axon telodendria). The cell morphology and application sites are illustrated in the center photograph. The cell was clamped at potentials ranging from -70 to +40 mV, in 10 mV steps. Glutamate was applied by pressure ejection in 100 msec pulses. Responses on the left were obtained in Co^{2+}-substituted Ringer's solution (with 0 mM Ca^{2+}), and the responses on the right were obtained in normal Ringer's. Glutamate application at the OPL (top traces) elicited a conductance increase associated with a reversal potential near -6 mV. IPL application (bottom traces) elicited no response in Co^{2+} Ringer's, but generated a conductance increase associated with a reversal potential near -46 mV in normal Ringer's. E_{Cl} was -50 mV in this experiment.

the NMDA types (Mittman *et al.*, 1990; Hensley *et al.*, 1993). Application of GABA to the retina suppresses surround light responses in subpopulations of bipolar cells (Kondo & Toyoda, 1982; Wu, 1986; Stone & Schutte, 1991), and it exerts postsynaptic actions on cones by activating $GABA_A$ receptors (Tachibana & Kaneko, 1984; Kaneko & Tachibana, 1986; Wu, 1991b). GABA also activates chloride conductances and modulates calcium currents in bipolar cells (Attwell *et al.*, 1987; Lukasiewicz *et al.*, 1994; Heidelberger & Mathews, 1992).

In this article, we present studies on the glutamatergic and GABAergic inputs to retinal bipolar cells. Since glutamate and GABA receptors are present in both plexiform layers, we compared the postsynaptic actions of these two neurotransmitters in the OPL and IPL. We applied glutamate and GABA with focal puff pipettes at the OPL and IPL under visual guidance in the retinal slice preparation. This approach allowed us to differentially examine the glutamatergic or GABAergic inputs to bipolar cells in the OPL (from photoreceptors and horizontal cells, respectively) and in the IPL (from bipolar cells and amacrine cells, respectively).

MATERIALS AND METHODS

Bipolar cells in salamander (*Ambystoma tigrinum*) retinal slices (Werblin, 1978) were voltage clamped with patch electrodes. Series resistances were typically 20 MΩ. The patch electrodes contained 69 mM Cs_2SO_4 and 15.7 mM CsCl (for $E_{Cl} = -50$ mV), or 63 mM Cs_2SO_4 and 24.3 mM CsCl (for $E_{Cl} = -40$ mV), and 2 mM EGTA, 1 mM $MgCl_2$, 0.1 mM $BaCl_2$ (to improve sealing), 1 mM ATP, 0.5 mM GTP, 1 mM Hepes, 0.8 mM Lucifer Yellow, adjusted to pH 7.2 with CsOH. The bathing medium contained 120 mM NaCl, 2.5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 5 mM HEPES, and 5 mM glucose, adjusted to pH 7.7 with NaOH. In some experiments 2 mM $CoCl_2$ was substituted for $CaCl_2$ in order to suppress presynaptic calcium influx. Glutamate or GABA was applied focally to the bipolar cell dendritic and axonal terminal regions by pressure ejection from micropipettes with a lumen of about 1 μm. Glutamate was applied to 317 bipolar cells in this study, and GABA to 78 cells. The cells were characterized morphologically by Lucifer Yellow fluorescence, and categorized by the level at which their axons ramified within the IPL.

RESULTS

Lucifer Yellow fills revealed that bipolar cell axons give rise to telodendria ramifying over a radius of 10–120 μm in the IPL. These telodendria were narrowly stratified at various levels within the IPL. Most bipolar cells had telodendria ramifying at a single level, but bistratified and tristratified cells accounted for 15 and 1%, respectively, of the cells visualized. Two types of dendritic glutamate response were observed in bipolar cells, and these were strictly correlated with the level of stratification. Cells with excitatory responses to glutamate (the off-center cells, or HBCs) had telodendria stratified within the distal 55% of the IPL (sublamina a). Cells with hyperpolarizing responses to glutamate (the on-center cells, or DBCs) had telodendria ramifying within the proximal 45% of the IPL (sublamina b). Only 12% of the multistratified bipolar cells observed had telodendria stratified in both sublamina a and sublamina b. The four such cells for which we have glutamate response data gave excitatory dendritic responses similar to those of the HBCs which ramified exclusively in sublamina a.

Figure 1 shows the current responses of an HBC to focal application of 100 μM glutamate at the OPL (location 1) and IPL (location 2), when the cell was clamped at potentials ranging from −70 to +40 mV, in 10 mV increments. The left column shows current responses to glutamate recorded in Ringer's solution containing 2 mM Co^{2+} (0 mM Ca^{2+}), and the right column shows responses recorded in normal Ringer's. Glutamate applied at the OPL (near the HBC dendrites) elicited an inward current when the HBCs were voltage clamped near the dark membrane potential [−40 mV, Yang & Wu (1993)]. Similar results were obtained in Co^{2+} Ringer's, where Ca^{2+}-dependent synaptic inputs were disrupted, and in normal Ringer's solution, where synaptic inputs to the bipolar cells were intact, except that in normal Ringer's the current responses sometimes appeared biphasic, possibly due to glutamate-induced synaptic transmission from other cells (see Discussion section). The initial current responses, however, had nearly identical properties (i.e. time course and reversal potential) under both conditions. The mean reversal potential for this current in HBCs was -4.7 ± 3.4 mV. This suggests that the HBC glutamate response is caused by the opening of cation channels at the dendrites, and such a conductance mechanism is consistent with the properties of kainate/AMPA receptors. In Co^{2+} Ringer's, glutamate applied at the IPL (near the axon telodendria) produced no current in the HBCs, suggesting that postsynaptic glutamate receptors do not exist on the telodendria. In normal Ringer's, however, focal glutamate application at the IPL in normal Ringer's generated an inward current when the cell was clamped at potentials negative to the chloride equilibrium potential (E_{Cl}), and this current reversed near (E_{Cl}). A similar conductance increase could be elicited by IPL application of 100 μM kainate, but not by 1 mM D-aspartate (not shown). Since this current was not observed in Co^{2+} Ringer's, it is likely that glutamate applied at the IPL activated glutamate receptors in other neurons that were presynaptic to the HBC. These neurons then released neurotransmitter substances which opened chloride channels in the HBC.

Figure 2 shows similar data for a DBC. In these cells OPL glutamate application elicited a current that was outward at potentials negative to the reversal potential (-11.4 ± 3.9 mV), indicating that glutamate caused a conductance decrease by closing cation channels. This is consistent with the presence of L-AP4 receptors on the DBC dendrites. The dendritic responses for DBCs tended

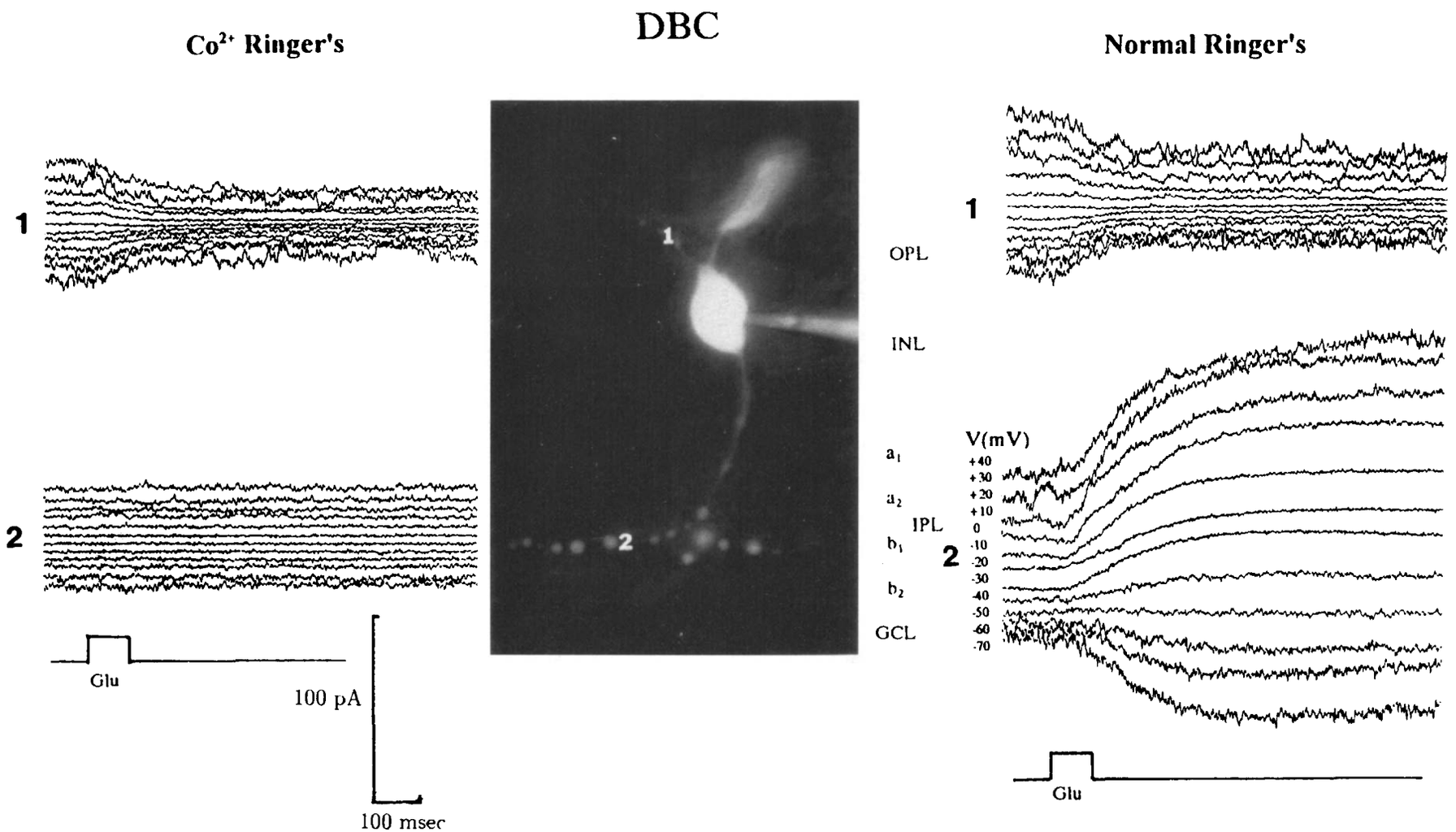

FIGURE 2. Current responses of an on-center bipolar cell (DBC) to focal pressure ejection of 100 μM glutamate at the OPL (location 1) and IPL (location 2). Experimental protocol and data presentation are identical to that in Fig. 1. At the OPL (top traces) glutamate elicited a conductance decrease associated with a reversal potential near -11 mV. IPL application (bottom traces) elicited no response in Co^{2+} Ringer's, but generated a conductance increase associated with a reversal potential near -40 mV in normal Ringer's. E_{Cl} was -40 mV in this experiment.

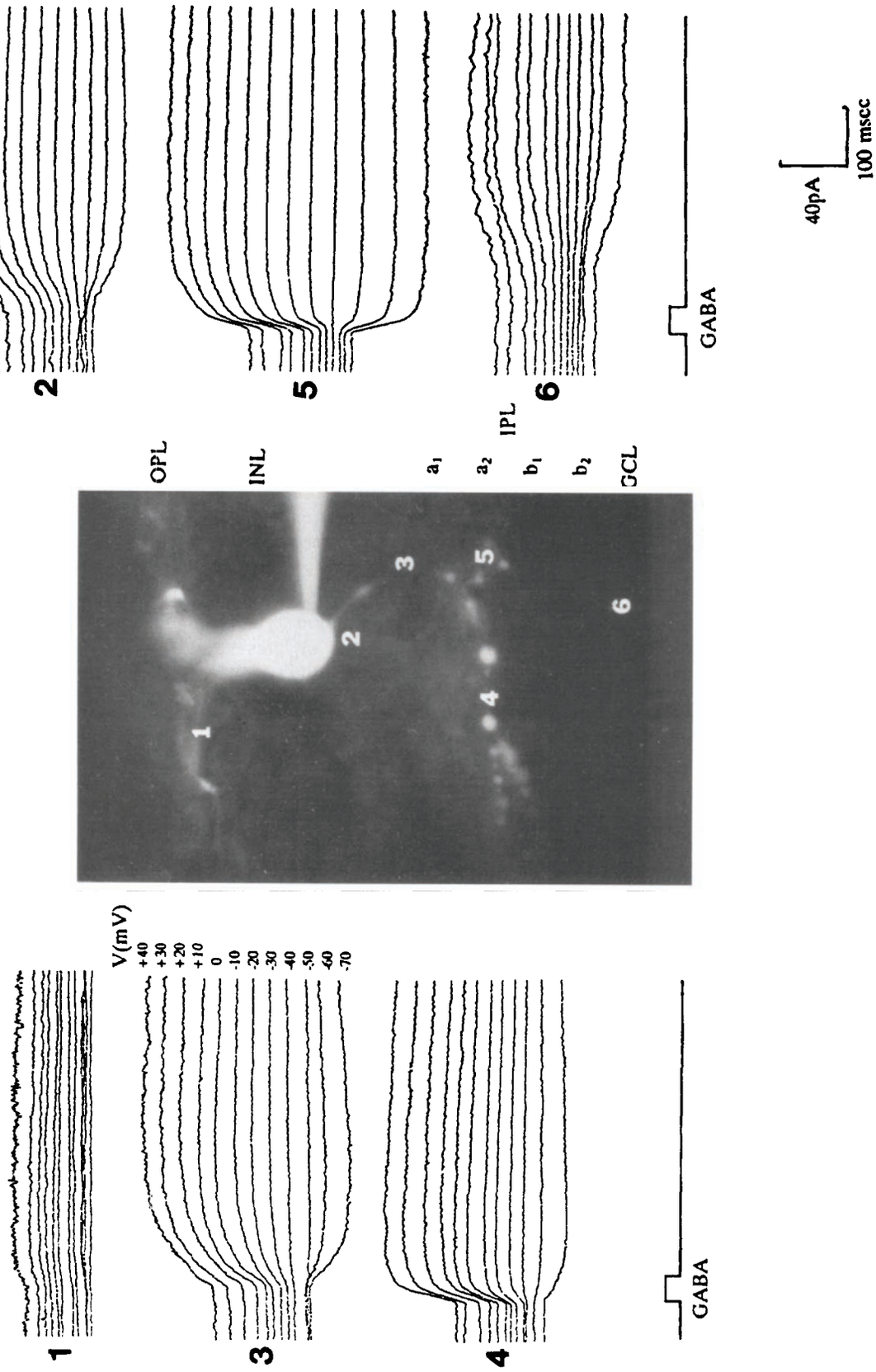

FIGURE 3. Current responses of an *off-center bipolar cell to focal application of 100 μM* GABA at various locations (indicated by the numbers in the center photograph). At each location responses were obtained for holding potentials ranging from −70 to +40 mV. Responses were largest and fastest for application near the axon telodendria (locations 4 and 5 in IPL sublamina a). Smaller responses with a longer time to peak were obtained for applications at the inner cellular layer (locations 2 and 3) and ganglion cell layer (location 6). Little response was observed for applications near the dendrites in the OPL (location 1). The responses reversed near E_{Cl}, which was set to −50 mV in this experiment.

to be weaker than for the HBCs and were sometimes absent, possibly because the cGMP cascade associated with the L-AP4 receptors in those cells is more sensitive to internal dialysis by the patch electrodes. As for the HBCs, in the presence of cobalt there was no IPL glutamate response, suggesting the absence of glutamate receptors on the DBC telodendria. Also as for the HBCs, IPL application of glutamate elicited a chloride conductance increase in normal Ringer's, again probably the result of synaptic input from amacrine cells. The mean reversal potential of the IPL glutamate response for all bipolar cells studied was -48.5 ± 1.3 mV (for $E_{Cl} = -50$ mV), and -38.0 ± 1.5 mV (for $E_{Cl} = -40$ mV).

One neurotransmitter likely to contribute to the IPL glutamate responses is GABA. GABA has been previously shown to activate a bicuculline resistant chloride conductance in salamander bipolar cells (Lukasiewicz *et al.*, 1994). Figure 3 shows current responses of an HBC to focal application of 100 μM GABA in Co^{2+} Ringer's solution at the OPL (location 1), at the base of the cell body (location 2), near the axon (location 3), at the IPL (locations 4 and 5) and at the ganglion cell layer (location 6) (the cell morphology and GABA application sites are shown in the center photograph). GABA applied at the OPL (location 1, near the HBC dendrites) elicited no current, indicating that there were few or no GABA receptors on the HBC dendrites. Application of GABA at the IPL (at locations 4 and 5), on the other hand, produced large postsynaptic currents with a fast rise time (the time-to-peak was about 100 msec), indicating that GABA receptors were very close to these sites (the axon telodendria region of the HBC). Applications of GABA at locations 2, 3, and 6 also produced noticeable currents, but their time course was much slower (the time-to-peak was usually 300 msec or longer). This suggests that the GABA receptors were farther away from these three locations, and the current responses were probably elicited by GABA diffusing from these application sites to the IPL. The GABA-induced postsynaptic currents exhibited a reversal potential near E_{Cl}, and they were associated with a conductance increase. These results are consistent with the notion that GABA opens chloride channels by activating postsynaptic GABA receptors on bipolar cell axon terminals. GABA elicited chloride conductance increases in 97% of the bipolar cells studied, and the mean reversal potential for the GABA induced current was -47.8 ± 1.6 mV (for $E_{Cl}=-50$ mV) and -39.4 ± 2.4 mV (for $E_{Cl}=-40$ mV). Similar response profiles were obtained for both HBCs and DBCs, with GABA sensitivity always restricted to the IPL. Similar profiles were also obtained in normal Ringer's solution or Ringer's with Ca^{2+} replaced by 2 mM Cd^{2+} or 20 mM Mg^{2+}, so the absence of a dendritic GABA response cannot be attributed to a Co^{2+}-dependent block of GABA receptors.

These studies suggest that GABA receptors are probably located primarily at the axon terminal regions and not on the dendrites of bipolar cells in the tiger salamander retina. In this paper we have not made a critical pharmacological comparison between the GABA- and glutamate-elicited chloride conductances, because we have not yet found an effective, selective antagonist for the bicuculline-resistant GABA receptors found in these cells.

DISCUSSION

Results described in this article indicate that glutamate receptors are located on the dendrites but not on the axon telodendria of retinal bipolar cells. GABA receptors, on the other hand, are distributed primarily at the IPL near the axon telodendria, but not on dendrites of the bipolar cells. These results lead to several issues in retinal circuitry that deserve discussion.

1. Our data show that postsynaptic glutamate receptors exist only on the dendrites of bipolar cells, where the photoreceptor synapses are made. There are no glutamate-gated cation channels at the bipolar cell axon terminals; therefore, glutamate released from bipolar cells does not polarize the presynaptic terminals (i.e. there is no autofeedback) in the IPL.
2. Although application of glutamate to the IPL does not produce any current in Co^{2+} Ringer's, it elicits chloride currents in normal Ringer's. This suggests that glutamate is generating inhibitory synaptic transmission to bipolar cells by acting at glutamate receptors on presynaptic inner plexiform neurons. The most likely candidates for such neurons are the GABAergic and glycinergic amacrine cells (Werblin *et al.*, 1988; Wu, 1991a; Yang *et al.*, 1991). GABA and glycine are known to open chloride channels in bipolar cells [Attwell *et al.* (1987); Lukasiewicz *et al.* (1994); Maple & Wu (in preparation) also see Fig. 3]. In the IPL glutamate depolarizes GABAergic and/or glycinergic amacrine cells, causing the release of GABA and/or glycine and the activation of chloride conductances in bipolar cells.
3. An alternate possibility for the glutamate-induced chloride current in the IPL is that it is mediated by a Co^{2+}-sensitive glutamate-gated chloride conductance at the bipolar cell axon terminals. Glutamate activates a chloride conductance in cone synaptic terminals (Sarantis *et al.*, 1988; Tachibana & Kaneko, 1988), and in the perch retina glutamate opens chloride channels at the dendrites of cone-driven on-center bipolar cells (Grant & Dowling, 1995). These glutamate-gated channels, however, are strongly activated by D-aspartate and not by kainate. We have found that IPL application of kainate strongly elicits chloride conductances in salamander bipolar cells, while D-aspartate has little effect. This does not correspond to the pharmacology of any known glutamate-gated chloride channels.
4. Our finding that GABA elicits no postsynaptic currents at the OPL suggests that $GABA_A$ and $GABA_C$ receptors (and thus chloride-mediated

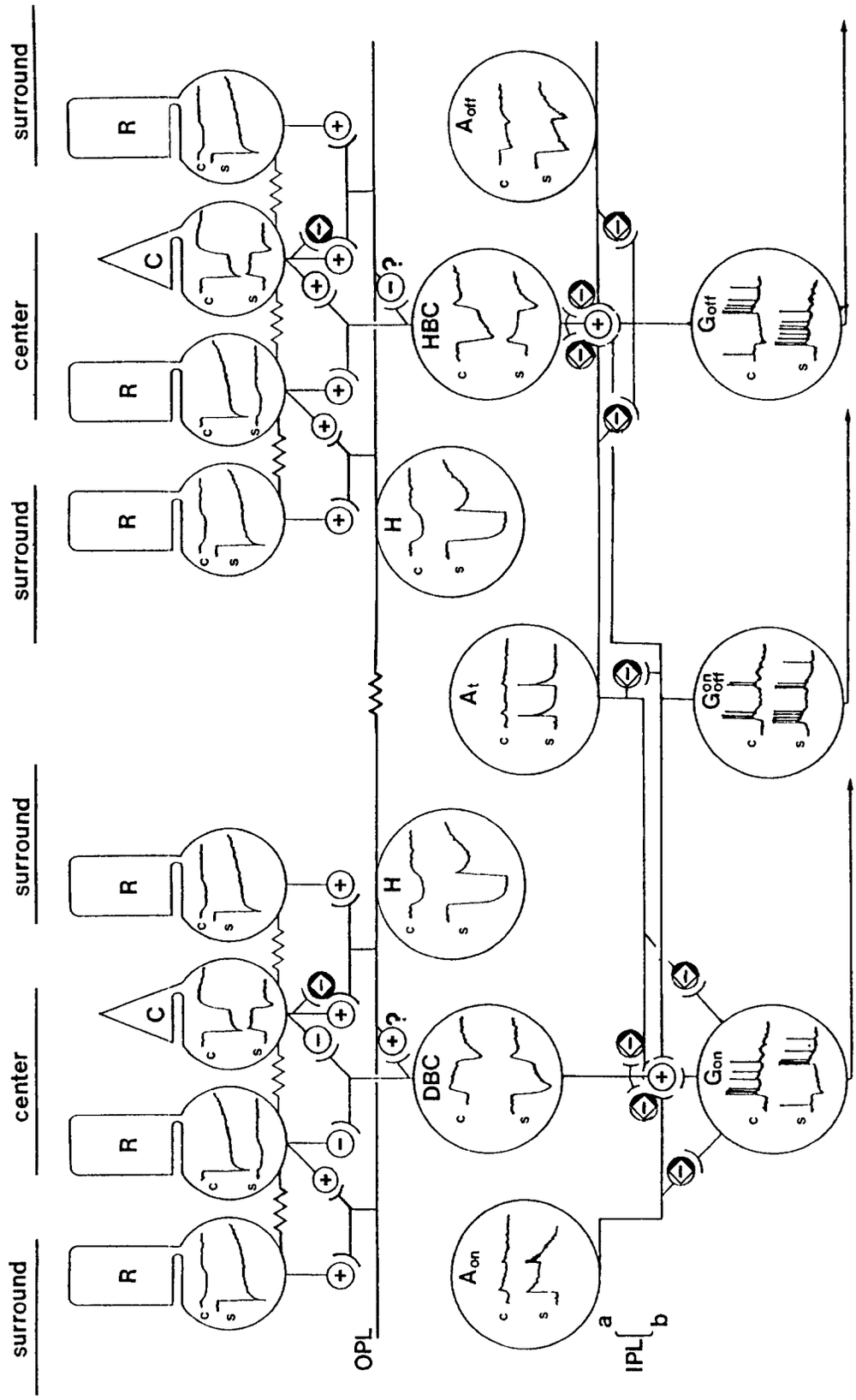

FIGURE 4. Schematic diagram of major connections and light responses in the tiger salamander retina. R, rod; C, cone; DBC, depolarizing bipolar cell; HBC, hyperpolarizing bipolar cell; H, horizontal cell; A_{on}, sustained on (slowly decaying) amacrine cell; A_t, transient (rapidly decaying) amacrine cell; A_{off}, sustained off amacrine cell; G_{on}, on-center ganglion cell; G_{off}^{on}, on–off ganglion cell; G_{off}, off-center ganglion cell; +, sign preserving chemical synapse; −, sign-inverting chemical synapse; ⏦, electrical synapse; ○, glutamatergic synapse; ◆, GABAergic synapse; ◇, glycinergic synapse. The upper trace in each circle illustrates the voltage response recorded intracellularly in that cell type when the center of the cell's receptive field is stimulated with light, and the lower trace shows the voltage response to surround illumination.

GABAergic synapses by horizontal cells) do not exist on bipolar cell dendrites. Morphological evidence has indicated that feedforward synapses exist between horizontal cells and bipolar cells (Dowling & Werblin, 1969; Lasansky, 1973), but our data suggest that these synapses are either not GABAergic, or, if GABAergic, do not involve a chloride conductance mechanism. In the tiger salamander retina, autoradiographic and immunocytochemical studies have shown that only about 60% of the horizontal cell somata are labeled with GABA and the neurotransmitter used by the remaining 40% is uncertain [but not glycine, Wu (1986, 1991a); Yang *et al.* (1991)]. It is possible that GABAergic horizontal cells make feedback synapses on cones (Wu, 1991b) and the nonGABAergic horizontal cells make feedforward synapses on bipolar cells. Further experiments are needed to clarify this issue.

5. We have shown in Fig. 1 that at potentials far from E_{Cl} the OPL glutamate responses in normal Ringer's solution appeared more sustained than in Co^{2+} Ringer's. In addition to the initial component, the currents recorded in normal Ringer's exhibited a second delayed component. The absence of this delayed component in Co^{2+} Ringers suggests that it was mediated by the actions of glutamate on other neurons that send synaptic inputs to the bipolar cell. The axons of the bipolar cells we studied were sometimes severed in the slicing procedure, and in such axotomized cells we never observed this delayed inhibition. It seems likely, therefore, that this inhibition represents an amacrine cell input to the bipolar cell telodendria, rather than a horizontal cell input to the bipolar cell dendrites. Although feedforward antagonism of bipolar cells by horizontal cells has been inferred from light response studies (Yang & Wu, 1991; Hare & Owen, 1992), our voltage clamp studies in retinal slices have not yielded support for such a mechanism. At the same time, our results suggest that inhibition from amacrine cells may contribute significantly to the surround antagonism seen in bipolar cell light responses. It is possible that horizontal cells inhibit bipolar cells by an unusual mechanism not observable by the methods used in this study.

Based on the results described in this article, and those in previous publications [for review, see Wu (1994)], a schematic diagram summarizing major synaptic connections mediating the center–surround receptive fields of the DBCs and HBCs in the tiger salamander retina is given in Fig. 4. Voltage responses to center light stimuli (C) are shown in upper traces and responses to surround light stimuli (S) are shown in the lower traces in each cell. Glutamatergic synapses are labeled as circles: these include all photoreceptor output synapses in the OPL and bipolar cell output synapses in the IPL. GABAergic synapses are labeled as diamond-in-circles with filled margins: these include the feedback synapse from horizontal cells to cones in the OPL and synapses from amacrine cells to bipolar cell axon terminals in the IPL. Glycinergic synapses are labeled as diamond-in-circles with open margins: these include synapses from amacrine cells to bipolar cell axon terminals in the IPL (Smiley & Yazulla, 1990; Attwell *et al.*, 1987; Maple & Wu, in preparation). The identity of the neurotransmitter used by the feedforward synapses from horizontal cells to bipolar cells is unknown, and therefore these synapses are labeled with questions marks.

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